

Response and Amendment under 37 C.F.R. § 1.111
Application No. 09/516,194

William Tam be deleted as inventors of the application and acknowledge that Manuel Worcel's and Sang William Tam's invention is no longer claimed. The amendment under 37 CFR § 1.48(b) is signed by Gordon Letts, Ph.D., a representative of NitroMed, Inc., the assignee of the present application.

III. Restriction Requirement

The Office Action states that claims 1, 9, 18, 32, 41-103 and 107-115 are withdrawn from consideration pursuant to 37 C.F.R. § 1.142 (b) as drawn to non-elected inventions.

Applicants respectfully submit that claim 1 is directed to the elected invention. Claim 2 discloses compounds of Formula I that are nitrosated prostaglandins (i.e., contain a -NO₂ group); nitrosylated prostaglandins (i.e., contain a -NO group), or nitrosated and nitrosylated prostaglandins (i.e., contain a -NO₂ group and a -NO group). Claim 1 is directed to compounds that are nitrosylated prostaglandins and is encompassed within the scope of claim 2.

Applicants note that if the election of species requirement is maintained, Applicants respectfully request the examination of additional species upon an indication of the allowability of the elected species pursuant to M.P.E.P. 803.02. In particular, it is noted that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended [to the non-elected species]....The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim." M.P.E.P. 803.02.

In view of the above, Applicants respectfully request rejoinder and examination of claim 1 with the pending claims.

IV. Rejection under 35 U.S.C. §112, second paragraph

Claim 1¹ is rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claim 2 has been amended to delete the proviso for "ethylene glycol mononitrates" as suggested by the Examiner. In view thereof, Applicants respectfully request that the rejection under this provision be withdrawn.

V. Misjoinder of Inventions

Claims 2-8, 10-17, 19-31, 33-40 and 104-106 are objected to as being directed to misjoinder of inventions.

Applicants respectfully submit that pending claims 1-8, 10-17, 19-31, 33-40 and 104-106 all fall within the scope of the Applicants election of Group II of the Examiner's Restriction

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Requirement dated May 8, 2001. All the pending claims are directed to compositions and kits comprising a compound of Formula I and their methods of use for the treatment of sexual dysfunctions.

In view of the above, Applicants respectfully request that the rejection under this provision be withdrawn.

VI. Conclusion

Applicants respectfully request reconsideration and allowance of pending claims 1-8, 10-17, 19-31, 33-40 and 104-106.

Examiner Gerstl is encouraged to contact the undersigned at 202-942-8453 concerning any questions about the present application

Respectfully submitted

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Dated: October 24, 2001

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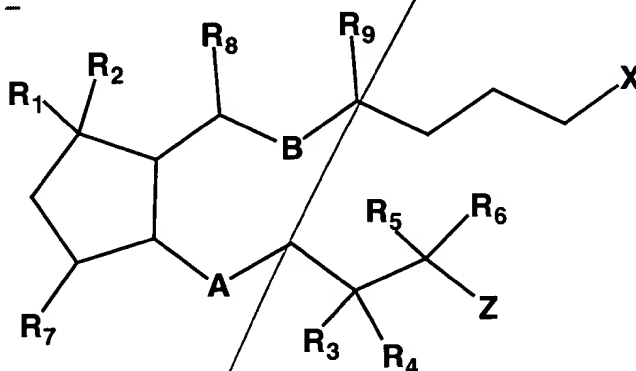
¹ Applicants assume this is a typographical error and that the Examiner intended to refer to claim 2.

Appendix 1 Pending Claims

What is claimed is:

1. A prostaglandin comprising at least one NO group or a pharmaceutically acceptable salt thereof.

2. (Twice Amended) A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is:



wherein the dotted lines indicate a single or a double bond;

R₁ is -OD₁ or -Cl;

R₂ and R₈ are a hydrogen ; or R₁ and R₂ taken together are =CH₂ or =O;

R₃ and R₄ are each independently a hydrogen, -OD₁ or -CH₃ ;

R₅ and R₆ are each independently a hydrogen, -OD₁, -CH₃ , -OCH₃ or -CH=CH₂;

R₇ is a hydrogen or -OD₁;

R₉ is hydrogen or absent when the carbon to which it is attached is the central carbon of an allene functionality; or R₈ and R₉ taken together with the chain to which they are attached form a substituted benzene ring with the proviso that R₁ is an oxygen atom which is attached to the carbon atom at the position of the benzene ring defined by B;

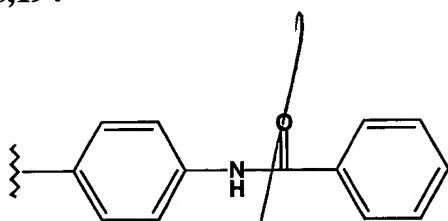
A is -CH=, -CH₂, -S-, or -O-;

B is -CH=, -CH₂, -S-, or -C(O)-;

X is -CH₂OR₁₁, -C(O)OR₁₁ or -C(O)N(D₁)R₁₂;

R₁₁ is D₁, a lower alkyl group, or

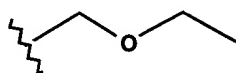
a¹
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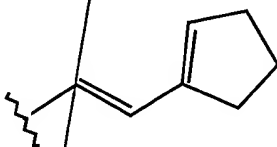
R_{12} is $-S(O)_2CH_3$ or $-C(O)CH_3$;

Z is (a) an ethyl, (b) a butyl, (c) a hexyl, (d) a benzyl,

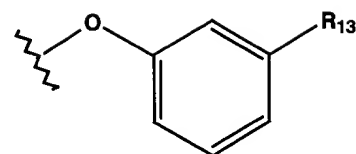
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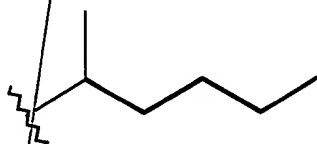


(g)



(h)

or



R_{13} is a hydrogen or $-Cl$;

D_1 is a hydrogen or D; with the proviso that at least one D_1 in formula (I) must be D;

D is Q or K;

Q is $-NO$ or $-NO_2$;

K is $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-T-Q$;

with the proviso that when X is $-C(O)OD_1$ and D_1 is K, then K is not an alkyl, branched alkyl or cycloalkyl mononitrate; a benzoic acid substituted benzyloxy mononitrate; a polyethylene glycol mononitrate; the regioisomeric esters of glycerol dinitrate and oligomers thereof;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently $-C(O)-$, $-C(S)-$, $-T-$, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_{q-}$;

E at each occurrence is independently $-T-$, an alkyl group, an aryl group, $-(C(R_e)(R_f))_h-$, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_{q-}$;

h is an integer from 1 to 10;

q is an integer from 1 to 5;

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R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, an alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $(C(R_e)(R_f))_k$ -T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group;

k is an integer from 1 to 3;

T at each occurrence is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-;

o is an integer from 0 to 2;

R_a is a lone pair of electrons, a hydrogen or an alkyl group;

R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂)⁻•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_i is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂)⁻•M⁺, or R_e or R_f are T-Q or $(C(R_e)(R_f))_k$ -T-Q, then the "-T-Q" subgroup can be a hydrogen, an alkyl, an alkoxy, an alkoxyalkyl, an aminoalkyl, a hydroxy, a heterocyclic ring or an aryl group.

3. (Amended) The compound of claim 2, wherein the compound comprising at least one NO group, at least one NO₂ group, or at least one NO and NO₂ group is a nitrosated arbaprostil, a nitrosylated arbaprostil, a nitrosated and nitrosylated arbaprostil, a nitrosated

Appendix 1

*a¹
cont*

alprostadil, a nitrosylated alprostadil, a nitrosated and nitrosylated alprostadil, a nitrosated beraprost, a nitrosylated beraprost, a nitrosated and nitrosylated beraprost, a nitrosated carboprost, a nitrosylated carboprost, a nitrosated and nitrosylated carboprost, a nitrosated cloprostenol, a nitrosylated cloprostenol, a nitrosated and nitrosylated cloprostenol, a nitrosated dimoxaprost, a nitrosylated dimoxaprost, a nitrosated and nitrosylated dimoxaprost, a nitrosated enprostil, a nitrosylated enprostil, a nitrosated and nitrosylated enprostil, a nitrosated enisoprost, a nitrosylated enisoprost, a nitrosated and nitrosylated enisoprost, a nitrosated fluprostenol, a nitrosylated fluprostenol, a nitrosated and nitrosylated fluprostenol, a nitrosated fenprostalene, a nitrosylated fenprostalene, a nitrosated and nitrosylated fenprostalene, a nitrosated gemeprost, a nitrosylated gemeprost, a nitrosated and nitrosylated gemeprost, a nitrosated latanaprost, a nitrosylated latanaprost, a nitrosated and nitrosylated latanaprost, a nitrosated limaprost, a nitrosylated limaprost, a nitrosated and nitrosylated limaprost, a nitrosated meteneprost, a nitrosylated meteneprost, a nitrosated and nitrosylated meteneprost, a nitrosated mexiprostil, a nitrosylated mexiprostil, a nitrosated and nitrosylated mexiprostil, a nitrosated misoprostol, a nitrosylated misoprostol, a nitrosated and nitrosylated misoprostol, a nitrosated misoprost, a nitrosylated misoprost, a nitrosated and nitrosylated misoprost, a nitrosated misoprostol acid, a nitrosylated misoprostol acid, a nitrosated and nitrosylated misoprostol acid, a nitrosated nocloprost, a nitrosylated nocloprost, a nitrosated and nitrosylated nocloprost, a nitrosated ornoprostil, a nitrosylated ornoprostil, a nitrosated and nitrosylated ornoprostil, a nitrosated prostalene, a nitrosylated prostalene, a nitrosated and nitrosylated prostalene, a nitrosated PGE₁, a nitrosylated PGE₁, a nitrosated and nitrosylated PGE₁, a nitrosated PGE₂, a nitrosylated PGE₂, a nitrosated and nitrosylated PGE₂, a nitrosated PGF₁, a nitrosylated PGF₁, a nitrosated and nitrosylated PGF₁, a nitrosated PGF₂, a nitrosylated PGF₂, a nitrosated and nitrosylated PGF₂, a nitrosated rioprostil, a nitrosylated rioprostil, a nitrosated and nitrosylated rioprostil, a nitrosated rosaprostol, a nitrosylated rosaprostol, a nitrosated and nitrosylated rosaprostol, a nitrosated remiprostol, a nitrosylated remiprostol, a nitrosated and nitrosylated remiprostol, a nitrosated sulprostone, a nitrosylated sulprostone, a nitrosated and nitrosylated sulprostone, a nitrosated trimoprostil, a nitrosylated trimoprostil, a nitrosated and nitrosylated trimoprostil, a nitrosated tiiprostanide, a nitrosylated tiiprostanide, a nitrosated and nitrosylated tiiprostanide, a nitrosated unoprostone, a nitrosylated unoprostone, a nitrosated and nitrosylated unoprostone, a nitrosated viprostol, a nitrosylated viprostol, a nitrosated and nitrosylated viprostol or a mixture

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thereof.

4. A composition comprising the compound of claim 2 and a pharmaceutically acceptable carrier.
5. A method for treating a sexual dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 4.
6. The method of claim 5, wherein the patient is female.
7. The method of claim 5, wherein the patient is male.
8. The method of claim 5, wherein the composition is administered orally, by intracavernosal injection, by transurethral application, or by transdermal application.
10. The composition of claim 4, further comprising at least one vasoactive agent or a pharmaceutically acceptable salt thereof.
11. The composition of claim 10, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α -blocker, a β -blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a dopamine agonist, an opioid antagonist, an endothelin antagonist or a mixture thereof.
12. The composition of claim 10, wherein the vasoactive agent is an α -blocker or a phosphodiesterase inhibitor.
13. The composition of claim 12, wherein the α -blocker is phentolamine, prazosin, doxazosin, terazosin, yohimbine or moxislyte and the phosphodiesterase inhibitor is papaverine, zaprinast, sildenafil or IC 351, or a mixture thereof.
14. A method for treating a sexual dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 10.
15. The method of claim 14, wherein the patient is female.
16. The method of claim 14, wherein the patient is male.
17. The method of claim 14, wherein the composition is administered orally, by intracavernosal injection, by transurethral application or by transdermal application.
19. A composition comprising at least one compound of claim 2 or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.
20. The composition of claim 19, further comprising a pharmaceutically acceptable

carrier.

21. The composition of claim 19, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

22. The composition of claim 21, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

23. The composition of claim 21, wherein the S-nitrosothiol is:

- (i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;
- (ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; and
- (iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $(\text{C}(\text{R}_e)(\text{R}_f))_k\text{-T-Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂-)•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_i is

$-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$ or $-(\text{N}_2\text{O}_2^-)\cdot\text{M}^+$; then " $\text{T}-\text{Q}$ " can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

24. The composition of claim 19, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

25. The composition of claim 19, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

- (i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;
- (ii) a compound that comprises at least one $\text{O}_2\text{N}-\text{O}-$, $\text{O}_2\text{N}-\text{N}-$, $\text{O}_2\text{N}-\text{S}-$ or $-\text{O}_2\text{N}-\text{C}-$ group;
- (iii) a N-oxo-N-nitrosoamine having the formula: $\text{R}^1\text{R}^2-\text{N}(\text{O}-\text{M}^+)-\text{NO}$, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

26. The composition of claim 25, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

27. The composition of claim 25, wherein compound comprising at least one $\text{O}_2\text{N}-\text{O}-$, $\text{O}_2\text{N}-\text{N}-$, $\text{O}_2\text{N}-\text{S}-$ or $\text{O}_2\text{N}-\text{C}-$ group is an $\text{O}_2\text{N}-\text{O}-$ polypeptide, an $\text{O}_2\text{N}-\text{N}-$ polypeptide, an $\text{O}_2\text{N}-\text{S}-$ polypeptide, an $\text{O}_2\text{N}-\text{C}-$ polypeptide, an $\text{O}_2\text{N}-\text{O}-$ amino acid, $\text{O}_2\text{N}-\text{N}-$ amino acid, $\text{O}_2\text{N}-\text{S}-$ amino

acid, an O₂N-C-amino acid, an O₂N-O-sugar, an O₂N-N-sugar, O₂N-S-sugar, an O₂N-C-sugar, an O₂N-O-oligonucleotide, an O₂N-N-oligonucleotide, an O₂N-S-oligonucleotide, an O₂N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-C-hydrocarbon, an O₂N-O-heterocyclic compound, an O₂N-N-heterocyclic compound, an O₂N-S-heterocyclic compound or an O₂N-C-heterocyclic compound.

28. A method for treating a sexual dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 19.

29. The method of claim 28, wherein the patient is female.

30. The method of claim 28, wherein the patient is male.

31. The method of claim 28, wherein the composition is administered orally, by intracavernosal injection, by transurethral application or by transdermal application.

33. The composition of claim 19, further comprising at least one vasoactive agent or a pharmaceutically acceptable salt thereof.

34. The composition of claim 33, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α -blocker, a β -blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a dopamine agonist, an opioid antagonist, an endothelin antagonist or a mixture thereof.

35. The composition of claim 34, wherein the vasoactive agent is an α -blocker or a phosphodiesterase inhibitor.

36. The composition of claim 35, wherein the α -blocker is phentolamine, prazosin, doxazosin, terazosin, yohimbine or moxislyte and the phosphodiesterase inhibitor is papaverine, zaprinast, sildenafil or IC 351, or a mixture thereof.

37. A method for treating a sexual dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 33.

38. The method of claim 37, wherein the patient is female.

39. The method of claim 37, wherein the patient is male.

40. The method of claim 37, wherein the composition is administered orally, by intracavernosal injection, by transurethral application or by transdermal application.

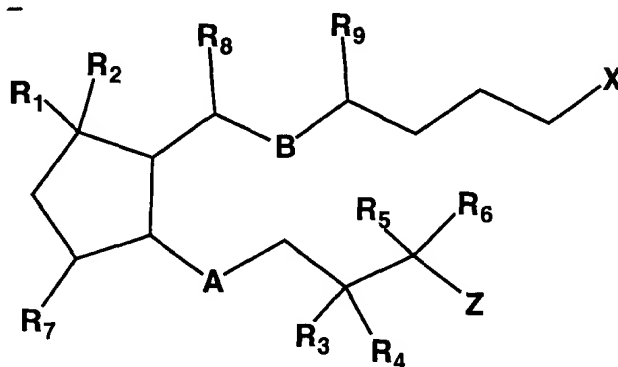
104. A kit comprising at least one compound of claim 2 and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

105. The kit of claim 104, wherein the compound of claim 2 and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase are separate components in the kit or are in the form of a composition in the kit.

106. The kit of claim 104, further comprising at least one vasoactive agent.

Appendix 2 – Amendments to Claims

2. (Twice Amended) A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is:



(I)

wherein the dotted lines indicate a single or a double bond;

R₁ is -OD₁ or -Cl;

R₂ and R₈ are a hydrogen ; or R₁ and R₂ taken together are =CH₂ or =O;

R₃ and R₄ are each independently a hydrogen, -OD₁ or -CH₃ ;

R₅ and R₆ are each independently a hydrogen, -OD₁, -CH₃, -OCH₃ or -CH=CH₂;

R₇ is a hydrogen or -OD₁;

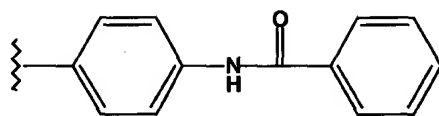
R₉ is hydrogen or absent when the carbon to which it is attached is the central carbon of an allene functionality; or R₈ and R₉ taken together with the chain to which they are attached form a substituted benzene ring with the proviso that R₁ is an oxygen atom which is attached to the carbon atom at the position of the benzene ring defined by B;

A is -CH=, -CH₂, -S-, or -O-;

B is -CH=, -CH₂, -S-, or -C(O)-;

X is -CH₂OR₁₁, -C(O)OR₁₁ or -C(O)N(D₁)R₁₂;

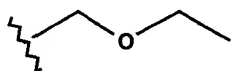
R₁₁ is D₁, a lower alkyl group, or



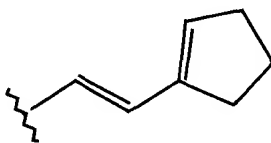
R_{12} is $-S(O)_2CH_3$ or $-C(O)CH_3$;

Z is (a) an ethyl, (b) a butyl, (c) a hexyl, (d) a benzyl,

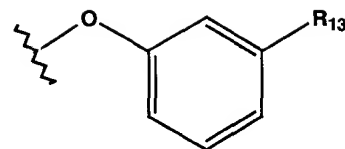
(e)



(f)

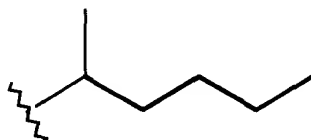


(g)



(h)

or



R_{13} is a hydrogen or $-Cl$;

D_1 is a hydrogen or D; with the proviso that at least one D_1 in formula (I) must be D;

D is Q or K;

Q is $-NO$ or $-NO_2$;

K is $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-T-Q$;

with the proviso that when X is $-C(O)OD_1$ and D_1 is K, then K is not an alkyl, branched alkyl or cycloalkyl mononitrate; a benzoic acid substituted benzyloxy mononitrate; [an ethylene glycol mononitrate;] a polyethylene glycol mononitrate; the regioisomeric esters of glycerol dinitrate and oligomers thereof;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently $-C(O)-$, $-C(S)-$, $-T-$, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_q-$;

E at each occurrence is independently $-T-$, an alkyl group, an aryl group, $-(C(R_e)(R_f))_h-$, a

Appendix 2

heterocyclic ring, an arylheterocyclic ring, or $-(\text{CH}_2\text{CH}_2\text{O})_q-$;

h is an integer from 1 to 10;

q is an integer from 1 to 5;

R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylaryl amino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, $-\text{T}-\text{Q}$, or $(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group;

k is an integer from 1 to 3;

T at each occurrence is independently a covalent bond, a carbonyl, an oxygen, $-\text{S}(\text{O})_o-$ or $-\text{N}(\text{R}_a)\text{R}_i-$;

o is an integer from 0 to 2;

R_a is a lone pair of electrons, a hydrogen or an alkyl group;

R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$, or $-(\text{N}_2\text{O}_2)^-\cdot\text{M}^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$ or $-(\text{N}_2\text{O}_2)^-\cdot\text{M}^+$, or R_e or R_f are $\text{T}-\text{Q}$ or $(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, then the " $-\text{T}-\text{Q}$ " subgroup can be a hydrogen, an alkyl, an alkoxy, an alkoxyalkyl, an aminoalkyl, a hydroxy, a heterocyclic ring or an aryl group.

3. (Amended) The compound of claim 2, wherein the compound comprising at least one NO group, at least one NO₂ group, or at least one NO and NO₂ group is a nitrosated arbaprostil, a nitrosylated arbaprostil, a nitrosated and nitrosylated arbaprostil, a nitrosated alprostadil, a nitrosylated alprostadil, a nitrosated and nitrosylated alprostadil, a nitrosated beraprost, a nitrosylated beraprost, a nitrosated and nitrosylated beraprost, a nitrosated carboprost, a nitrosylated carboprost, a nitrosated and nitrosylated carboprost, a nitrosated cloprostenol, a nitrosylated cloprostenol, a nitrosated and nitrosylated cloprostenol, a nitrosated dimoxaprost, a nitrosylated dimoxaprost, a nitrosated and nitrosylated dimoxaprost, a nitrosated enprostil, a nitrosylated enprostil, a nitrosated and nitrosylated enprostil, a nitrosated enisoprost, a nitrosylated enisoprost, a nitrosated and nitrosylated enisoprost, a nitrosated fluprostenol, a nitrosylated fluprostenol, a nitrosated and nitrosylated fluprostenol, a nitrosated fenprostalene, a nitrosylated fenprostalene, a nitrosated and nitrosylated fenprostalene, a nitrosated gemeprost, a nitrosylated gemeprost, a nitrosated and nitrosylated gemeprost, a nitrosated latanaprost, a nitrosylated latanaprost, a nitrosated and nitrosylated latanaprost, a nitrosated limaprost, a nitrosylated limaprost, a nitrosated and nitrosylated limaprost, a nitrosated meteneprost, a nitrosylated meteneprost, a nitrosated and nitrosylated meteneprost, a nitrosated mexiprostil, a nitrosylated mexiprostil, a nitrosated and nitrosylated mexiprostil, a nitrosated misoprostol, a nitrosylated misoprostol, a nitrosated and nitrosylated misoprostol, a nitrosated misoprost, a nitrosylated misoprost, a nitrosated and nitrosylated misoprost, a nitrosated misoprostol acid, a nitrosylated misoprostol acid, a nitrosated and nitrosylated misoprostol acid, a nitrosated nocloprost, a nitrosylated nocloprost, a nitrosated and nitrosylated nocloprost, a nitrosated ornoprostil, a nitrosylated ornoprostil, a nitrosated and nitrosylated ornoprostil, a nitrosated prostalene, a nitrosylated prostalene, a nitrosated and nitrosylated prostalene, a nitrosated PGE₁, a nitrosylated PGE₁, a nitrosated and nitrosylated PGE₁, a nitrosated PGE₂, a nitrosylated PGE₂, a nitrosated and nitrosylated PGE₂, a nitrosated PGF₁, a nitrosylated PGF₁, a nitrosated and nitrosylated PGF₁, a nitrosated PGF_{2□}, a nitrosylated PGF_{2□}, a nitrosated and nitrosylated PGF_{2□}, a nitrosated rioprostil, a nitrosylated rioprostil, a nitrosated and nitrosylated rioprostil, a nitrosated rosaprostol, a nitrosylated rosaprostol, a nitrosated and nitrosylated rosaprostol, a nitrosated remiprostol, a nitrosylated remiprostol, a nitrosated and nitrosylated remiprostol, a nitrosated sulprostone, a nitrosylated sulprostone, a nitrosated and nitrosylated sulprostone, a nitrosated trimoprostil, a nitrosylated trimoprostil, a nitrosated and nitrosylated trimoprostil, a

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nitrosated tiprostanide, a nitrosylated tiprostanide, a nitrosated and nitrosylated tiprostanide, a
nitrosated unoprostone, a nitrosylated unoprostone, a nitrosated and nitrosylated unoprostone, a
nitrosated viprostol, a nitrosylated viprostol, a nitrosated and nitrosylated viprostol or a mixture
thereof.

✓
Cancel claims 9, 18, 32, 41-103 and 107-115, without prejudice.